Genetic Predisposition and Depression Both Influence Teen Smoking

Research Findings
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NIDA-supported scientists have found that a gene, called *DRD2*, partly determines whether an adolescent who takes a first puff on a cigarette will progress to regular smoking. Adolescents who carry one of the two known forms of the gene (*A1*) are more likely than those with the other variant (*A2*) to become daily smokers. If the teen also suffers from depression, the genetic effect is amplified, further increasing the likelihood of smoking escalation, according to Dr. Janet Audrain-McGovern and colleagues at the University of Pennsylvania Transdisciplinary Tobacco Use Research Center (TTURC).

The new findings result from a large-scale study that Dr. Audrain-McGovern and her research group undertook to clarify outstanding issues surrounding *DRD2* and smoking. Scientists have suspected for some time that variations in *DRD2* might influence people's responses to tobacco, based on the gene's function: It helps guide construction of sites where the neurotransmitter dopamine—which plays a key role in producing the pleasurable effects of nicotine—attaches to brain cells. Some previous studies have found that, indeed, men and women who smoked or were nicotine-dependent were more likely to have the *A1 DRD2* variant than the *A2*. However, other studies did not confirm the link.

DRD2

Variants and Smoking Progression

Dr. Audrain-McGovern's team recruited 615 adolescents (322 girls, 293 boys) to participate in their study. Because genetic diversity would increase the difficulty of interpreting results, all the youths were of European ancestry. Analysis of DNA obtained from cheek swabs showed that the frequencies of the alternative *DRD2* forms, or alleles, were roughly the same among the participants as have been seen in general population samples of people of European stock: Two-thirds (67 percent) had inherited the *A2* allele from both parents, 30 percent had one *A1* and one *A2*, and 3 percent had two copies of the *A1*.

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The researchers interviewed the teens in ninth grade, asking questions used in the Youth Risk Behavior Survey, including, "Have you ever tried or experimented with cigarette smoking, even a few puffs?" "Have you smoked at least one whole cigarette?" "How many cigarettes have you smoked in the last 30 days?" and "How many cigarettes have you smoked in your lifetime?" Based on their responses, the teens were categorized as never smokers, puffers (a few puffs, but never a whole cigarette), experimenters (at least one but fewer than 100 lifetime cigarettes), and current smokers (smoked in the past 30 days and 100 or more lifetime cigarettes).

The teens answered the same questions again in the fall and spring of their 10th-grade year and in the spring of their 11th-grade year. Analyzing the teens' sequential responses together with their genetic data, the researchers found no association between variation in *DRD2* alleles and the likelihood that participants who had never smoked would start, Dr. Audrain-McGovern says. "However, among adolescents who had taken at least a single puff, we found a clear association between the *A1* allele and progressing up the ladder of smoking frequency—for example, moving from puffer to experimenter, or experimenter to current smoker. Each additional copy of the *A1* allele nearly doubled the odds of progression," she says. Among teens who had at least puffed once, those with a single *A1* allele were 1.8 times as likely, and teens who had inherited *A1* alleles from both parents were 3.4 times as likely as those with two *A2* alleles to progress to heavier smoking before they finished 11th grade.

"These results clearly illustrate the important interplay between a gene and the environment," Dr. Audrain-McGovern says. "The *DRD2* variant appears to play no role in whether or not these teens took that first puff. Its effect isn't seen until there is some biological exposure. Then, we see a markedly different response to nicotine, perhaps because the *A1* allele is associated with reduced density of dopamine receptors. If individuals with this allele have lower baseline levels of dopamine activity, they might experience greater reward when nicotine triggers an enhanced dopamine release."

DRD2 and Depression

During the ninth-grade interviews, the researchers administered the Center for Epidemiological Studies Depression Scale (CES-D Scale) to the study participants. Each teen rated how frequently he or she had experienced each of 20 depression symptoms during the past week. One hundred teens (16 percent) scored 23 or higher on this scale, which indicates clinically significant depression. Of the 100, 52 had at least one *A1* allele. Teens without an *A1* allele had an average CES-D score of 12.3; those with one *A1* and one *A2* had an average score of 15.1; and those with two copies of the *A1* allele averaged 16.7. There also was a significant association between the CES-D score and smoking status at the initial interview: The average score was 12.5 for never smokers, 14.6 for puffers, 13.7 for experimenters, and 20.8 for current smokers.

Teens with high depression scale scores and the *A1* allele were at the highest risk of smoking progression. Among teens with at least one *A1* allele, 33 percent of depressed teens, compared with 25 percent of nondepressed teens, reported smoking progression within 2 years.

The interaction of the *DRD2* allele and depression on smoking progression highlights the intricate interplay of genetic, psychological, and social factors that influence adolescents' smoking behavior, observes Dr. Allison Chausmer of NIDA's Division of Basic Neuroscience and Behavioral Research. "This research group has previously shown that adolescents who have depression are more receptive than nondepressed teens to the messages contained in tobacco advertising. This is not a trivial number of potential smokers. Roughly one in five high school students has symptoms that represent clinically significant depression. Those who succumb to the appeal of tobacco manufacturers' advertising and have this particular genetic makeup may be more likely to progress to higher levels of smoking and ultimately experience consequences of reduced health and longevity."

Source

- Audrain-McGovern, J., et al. Interacting effects of genetic predisposition and depression on adolescent smoking progression. *American Journal of Psychiatry* 161(7):1224-1230, 2004. [Full Text]

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